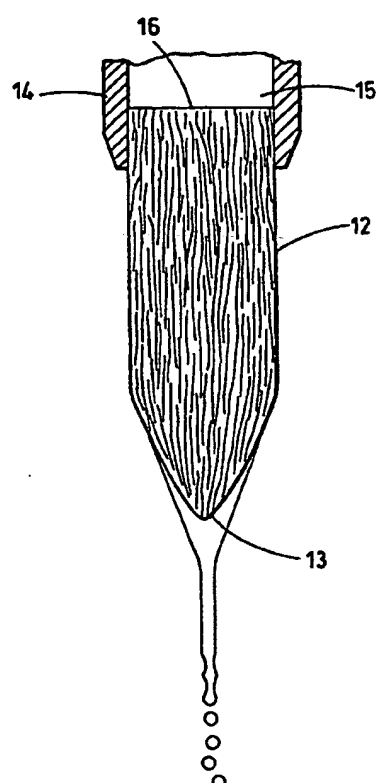


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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(21) International Application Number:</b> PCT/EP95/01163 <b>(22) International Filing Date:</b> 28 March 1995 (28.03.95) <b>(30) Priority Data:</b> 9406171.0 29 March 1994 (29.03.94) GB <b>(71) Applicant (for all designated States except US):</b> ELEC-TROSOLS LIMITED [GB/GB]; Thursley Copse, Farnham Lane, Haslemere, Surrey GU27 1HA (GB). <b>(72) Inventor; and</b> <b>(75) Inventor/Applicant (for US only):</b> COFFEE, Ronald, Alan [GB/GB]; Electrosols Limited, Thursley Copse, Farnham Lane, Haslemere, Surrey GU27 1HA (GB). <b>(74) Agent:</b> RUTTER, Keith; SmithKline Beecham, Corporate Intellectual Property, SB House, Great West Road, Brentford, Middlesex TW8 9BD (GB).		<b>(81) Designated States:</b> AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> DISPENSING DEVICE  <b>(57) Abstract</b> <p>A device for dispensing a comminuted liquid to the upper respiratory tract, which comprises an electrohydrodynamic comminution means and a means for supplying a liquid to the comminution means. And a device for comminuting a liquid, the comminution site (12) of which is provided by fibres projecting from an end surface or edge, the edge or surface being composed substantially of fibres.</p> 		

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## DISPENSING DEVICE

5 The invention relates to a dispensing device for comminuting a liquid and the use of such a device, in particular, in medicine.

Known nasal sprays generally produce droplet-sprays by mechanical means. The sprays so produced contain droplets within a broad range of droplet diameters which significantly reduces targeting accuracy and hence accuracy of dosing. The non-uniform nature of the sprays can also be very wasteful of  
10 medicament.

Dispensing devices are known which produce a finely divided spray of liquid droplets by electrostatic (more properly referred to as 'electrohydrodynamic') means. The droplet spray in such devices is generated by applying an electric field to a liquid at a spray head or spray edge. The  
15 potential of the electric field is sufficiently high to provide comminution of the liquid from the spray head. The droplets produced are electrically charged and thus are prevented from coagulating by mutual repulsion.

United Kingdom patent number 1569707 describes an electrohydrodynamic spray device principally for use in crop spraying. An  
20 essential component of the GB 1569707 spray device is a field intensifying electrode, cited adjacent the spray head. The field intensifying electrode is stated to reduce the incidence of corona discharge and allows lower electric field strengths to be used during spray generation.

US 4801086 discloses an electrohydrodynamic spray device which  
25 produces multiple spray streams.

United Kingdom patent number 2018627B discloses an electrohydrodynamic spray device wherein the droplet spray is fully or partially discharged by means of an earthed electrode having a sharp or pointed edge and located downstream of the spray head. The GB 2018627B spray device does  
30 not comprise the field intensifying electrode of GB 1569707.

European Patent number 0234842 discloses an inhaler which uses electrohydrodynamic spray technology. In use, the spray of charged droplets is discharged prior to inhalation by means of a sharp discharge electrode carrying an opposite charge to the droplet spray and located downstream of the spray  
35 head. The droplets are discharged so as to target droplet deposition into the

lower respiratory tract and to specifically avoid deposition of the droplets onto the mouth and throat of the user.

We have now discovered that electrohydrodynamic spray technology may be used to deliver charged or partially charged monodisperse liquid droplets sprays, especially medicament sprays, to the upper respiratory tract and especially to the nasal mucosa, in an efficient and very controllable manner.

Accordingly, there is provided a device for dispensing a comminuted liquid to the upper respiratory tract, which comprises an electrohydrodynamic comminution means and a means for supplying a liquid to the comminution means.

The electrohydrodynamic comminution means may be any conventional electrohydrodynamic comminution means, for example those described in the above mentioned patent specifications.

Suitably, the comminution means comprises a comminution site, usually a surface or edge and means for electrically charging the liquid at the said site to a potential sufficient to provide comminution of the liquid, the potential usually being of the order of 1-20 kilovolts.

One preferred comminution site is provided by fibres projecting from an end surface or edge, the edge or surface being composed substantially of fibres.

The surface or edge is conveniently provided by the end surface of a porous bundle of fibres.

A preferred surface or edge is provided by a cone or similar shape.

The fibres are suitably bonded together by a binding means to form the bundle but this is not essential, providing the bundle substantially maintains its shape and provides a suitable surface or edge to allow comminution of the liquid.

A suitable bonding means is a bonding polymer or resin.

Suitably the bundle is shaped into a rod shape, preferably having a cone shaped end which provides the comminution site.

The fibres are generally aligned coaxially within the bundle and are so aligned that liquid flows between the interstitial spaces defined by the fibres to the said comminution site.

It is envisaged that the fibrous comminution site can be used with any type of electrohydrodynamic device such as those disclosed in the above mentioned patent applications and also those disclosed in International Patent

Applications, Publication Numbers PCT/GB93/02443 and PCT/GB93/02634.

Accordingly, in a further aspect the invention provides a device for comminuting a liquid, which comprises an electrohydrodynamic comminution site, a means for supplying a liquid to the comminution site and a means for electrically charging the comminution site to an electric potential sufficient to comminute the liquid in use, characterized in that the comminution site is provided by fibres projecting from an end surface or edge, the edge or surface being composed substantially of fibres.

Suitable fibres are fibres of ceramic, glass, or polymer such as polyester or nylon. Suitable bundles of fibres are of the types commonly used in fibre tipped pens, an example of which is the Hewlett Packard product number T17847T.

The fibres herein may be of any length or thickness providing they are capable of allowing comminution of the liquid.

Conveniently, the fibrous comminution site is located in a conducting or semi conducting holding means.

A further preferred comminution surface or edge is a thin capillary tube or a slot defined by two parallel plates or concentric cylinders

The means for supplying a liquid formulation to the comminution means may be any appropriate mechanical or electrical liquid supplying means such as a syringe pump or an electrically powered pump as described in EP 0029301.

Preferably, the comminution means is adapted to provide liquid droplets having an average diameter of 10 microns or above, so as to further ensure that the droplets do not enter the lower respiratory tract. Droplets within the range of from 10 to 500 microns in diameter are particularly preferred, especially those within the range of from 10 to 200 microns.

For a given liquid the diameter of the charged droplets is suitably controlled by adjustment of the applied comminution voltage and liquid flow rate, using routine experimental procedures.

Liquids having viscosities within the range of from 1 to 500 centipoise and resistivities in the range of from  $10^2$  -  $10^8$  ohm m can be comminuted by the present device.

The device of the invention may be adapted into any embodiment form which dispenses comminuted liquid to the upper respiratory tract, for both medicinal and non-medicinal use.

Preferably, the device is in the form of nasal spray.

A suitable non-medicinal use includes the dispensing of a perfume or an aroma.

5 A suitable non-medicinal use includes the dispensing of a biocide or an insecticide.

Suitable liquids include liquid medicament formulations or liquid cosmetic formulations such as aroma formulations or perfume formulations.

A preferred liquid is a liquid medicament formulation.

10 Medicaments suitable for delivery by the device include those used for the treatment of disorders of the upper respiratory tract including disorders of the nasal mucosa, in particular congestion and disorders of the upper respiratory tract associated with hay fever. Medicaments suitable for delivery by the device also include those used for the treatment of sore throat.

15 Particular medicaments include nasal decongestants such as oxymetazoline, xylometazoline, phenylephrine, propylhexadrine, naphazoline and tetrahydrozoline and as appropriate salts thereof such as the hydrochloride salt, and formulations thereof. adapted for administration to the upper respiratory tract.

20 As described above electrohydrodynamic spray devices are known which produce multiple spray streams. However such devices are not known to be applied to the administration of liquid formulations. Accordingly, there is provided an electrohydrodynamic dispensing device for liquid formulations which comprises a mixing nozzle as described in USP4801086.

25 Thus, by inducing electric field turbulence, two or more liquid components can be mixed at the moment of delivery. This is an essential requirement for ingredients which would react too early if premixed. By reacting too soon before application, they may lose their intended properties or, for example the mixture may increase its viscosity so as to become unsprayable. Such an instantaneous mixing facility at the point and time of application of the mixture has not previously been possible.

30 Advantageously, the device of the invention, especially when in the form of a nasal spray, also comprises a means to partially electrically discharge the liquid comminution such that the residual charge on the comminution facilitates deposition of the comminution in the upper respiratory tract. The means to

partially discharge the comminution is conveniently that disclosed in United Kingdom patent number 2018627B

When used herein 'medicament' includes proprietary medicines, pharmaceutical medicines and veterinary medicines.

5 When used herein, unless more specifically defined herein, 'upper respiratory tract' includes the nasal mucosa.

The liquid medicinal formulations for use in the device of the invention may be formulated according to conventional procedures, such as those disclosed in the US Pharmacopoeia, the European Pharmacopoeia, 2nd Edition, 10 Martindale The Extra Pharmacopoeia, 29th Edition, Pharmaceutical Press and the Veterinary Pharmacopoeia.

The liquid cosmetic formulations for use in the device of the invention may be formulated according to conventional procedures, such as those disclosed in Harry's Cosmeticology, 9th Edition, 1982, George Goodwin 15 , London.

### **Specific Description of the Devices and Processes of the Invention**

#### **(1) Comminution sites**

20 Figure 1 shows a thin-walled capillary tube (1), made of conducting, semiconducting or electrically insulating material and electrically connected to a source of high-voltage direct-current, either directly or through the liquid. A single jet (3) is produced from a cusp (2) of liquid, both of which form naturally, according to the voltage and flow rate for a given liquid. Fig. 2 25 shows a conducting, semiconducting or insulating cylinder (1) which may have a larger diameter than those shown in fig. 1. This nozzle has an inner-member, (4) which is approximately coaxial with the outer tube, (1). Fig. 3 shows a slot nozzle, formed between two parallel plates (2) having conducting, semiconducting or insulating edges electrically connected to a high-voltage 30 direct-current supply, from which the liquid emerges, forming cusps and jets when the voltage supply and liquid flow rates are suitably adjusted according to the type of liquid being sprayed. For a given jet (and thus droplet) size, and a given liquid, this nozzle may enable a higher flow rate to be achieved than those in which a single cusp and jet are used.

Figure 7 shows a fibre tipped comminution site or nozzle (12) comprising a porous bundle of resin bonded fibres having a pointed tip (13). The bundle is held in an electrically conducting or semi conducting base (14) which also comprises a hollowed portion (15) forming a reservoir for the liquid. The liquid flows from the reservoir (15) to the base (16) of the fibre tipped bundle and thereafter flows through the bundle to the pointed tip (13).

The bundle is connected to a high voltage source, through the conducting or semi conducting base (14) or the bundle may be earthed through the base in the presence of an adjacent high voltage source, so as to create a high electric field at the pointed tip (13). When the voltage is applied the liquid at the pointed tip (13) forms into an electrohydrodynamic jet which subsequently breaks up, thus providing a spray of charged droplets.

## (2) Flow Inducers

An example of such a device is that illustrated in Fig. 4 which shows an ion stream flow inducer, wherein a high voltage electrode (5) breaks up pairs of charge carriers within the liquid, thus neutralizing those of opposite polarity at the electrode, and leaving a large population of monionized like-polarity charge carriers which stream away from the high voltage electrode by coulombic force, thus moving the liquid in the direction of the counter electrode (6) by means of viscous drag. This pumping means requires that an electrode (5) is able to effectively inject like-polarity charge carriers into the liquid, close to the electrode (5). This may be effectively done by using a sharp-edged conducting or semiconducting surface, held at a sufficiently high potential to disrupt lightly bonded charge carriers or to ionize the liquid. Normally, it is only possible to establish a strong enough field for both creating unipolar charge carriers and pumping the liquid, when the liquid is of sufficient resistivity. Typically a resistivity of, say 10 (exp. 8) ohm meters, will pump at several millilitre per minute, with a head of up to one meter, at a voltage of 10 to 20 kilovolts, and a direct current of only a few microamperes. More conductive liquids will draw more current and will establish a weaker electric field. Thus highly conducting liquids, such as, say tap water may not readily establish a practicable drag pressure.

## (3) Reactive Liquid Mixing



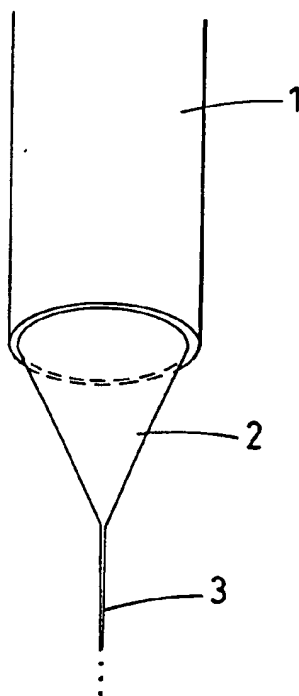
Two or more liquids may be mixed after emerging from the nozzle by maximizing turbulent motion which can be induced within the cusp (2) which forms the base of each liquid jet (3). Fig. 5 shows a nozzle formed by three parallel plates, forming two slot-gaps (7) through which two liquids, a and b, are induced to flow, and to subsequently become mixed in the cone-shaped liquid base (2) of each jet, in accordance with eddy currents that can be induced as shown. This mixing may be maximized by using a liquid formulation having the lowest possible viscosity for each liquid; the maximum nozzle potential; and an optimal flow rate and degree of asymmetry of the individual flow rates of the component liquids.

An alternative to the mixing arrangement of fig. 5 is shown in cross section in fig. 6, in which two coaxial cylinders (8) and (9) form two flow-channels (13) and (11). This arrangement has advantages and may induce a greater degree of mixing in some cases, for example, when there is a significant disparity in the flow rates of liquids a and b.

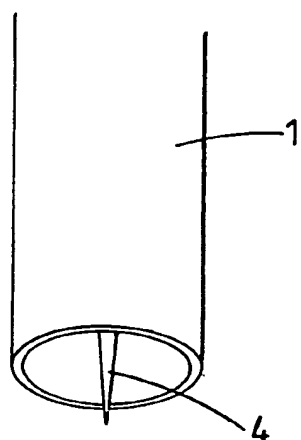
## Claims

1. A device for dispensing a comminuted liquid to the upper respiratory tract, which comprises an electrohydrodynamic comminution means and a means for supplying a liquid to the comminution means.
2. A device according to claim 1, wherein the comminution means comprises a comminution site and means for electrically charging the liquid at the said site to a potential sufficient to provide comminution of the liquid.
3. A device according to claim 2, wherein the comminution site is provided by a thin capillary tube or a slot defined by two parallel plates or concentric cylinders
4. A device according to claims 2 or 3, wherein the comminution site is provided by the end surface of a bundle of fibres, the fibres being so aligned that liquid flows along the length of the fibres and between the interstitial spaces defined by the fibres to the said end surface.
5. A device according to any one of claims 1 to 4, wherein the fibres are fibres of ceramic or polymer.
6. A device according to any one of claims 1 to 5, adapted to provide liquid droplets having an average diameter of 10 microns or above, so as to further ensure that the droplets do not enter the lower respiratory tract.
7. A device according to any one of claims 1 to 6, adapted to provide liquid droplets having an average diameter of within the range of from 10 to 500 microns in diameter.
8. A device according to any one of claims 1 to 7, in the form of a nasal spray.
9. A device according to any one of claims 1 to 8, adapted to dispense a biocide or an insecticide.

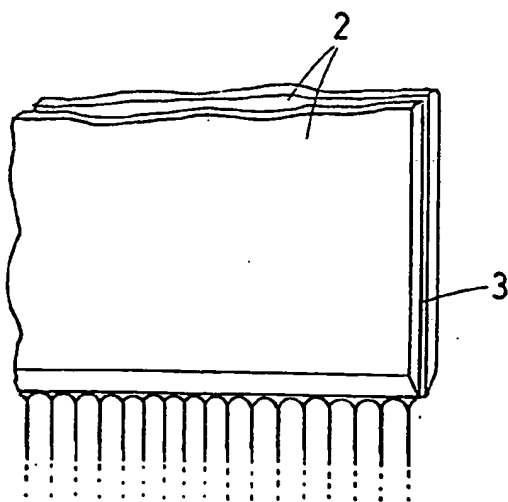
10. A device according to any one of claims 1 to 9, adapted to dispense a perfume or an aroma.
- 5 11. A device for comminuting a liquid, which comprises an electrohydrodynamic comminution site, a means for supplying a liquid to the comminution site and a means for electrically charging the comminution site to an electric potential sufficient to comminute the liquid in use, characterized in that the comminution site is provided by fibres projecting from an end surface  
10 or edge, the edge or surface being composed substantially of fibres.
12. A device according to claim 12, wherein the fibres are fibres of ceramic, glass, or apolymer such as polyester or nylon.



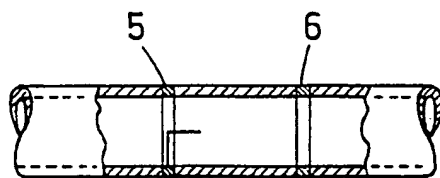
**Fig. 1**



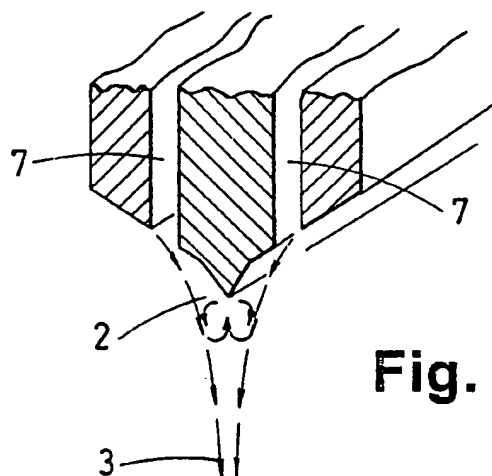
**Fig. 2**



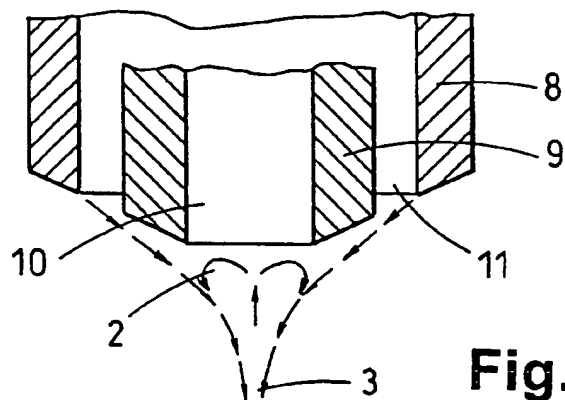
**Fig. 3**



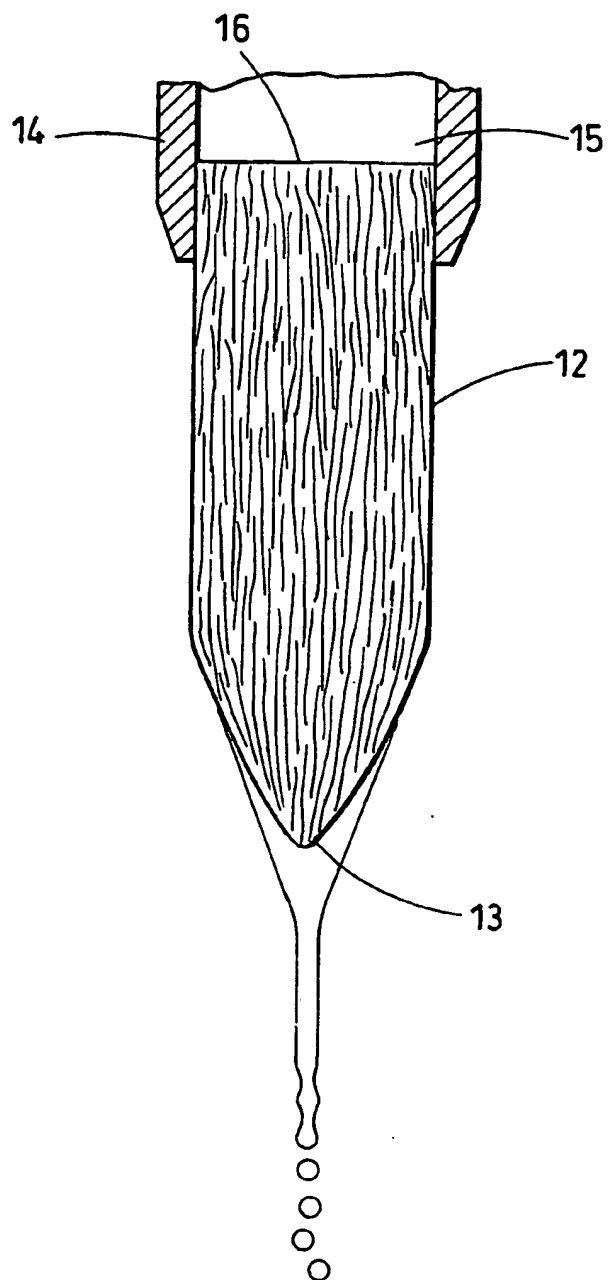
**Fig. 4**



**Fig. 5**



**Fig. 6**



**Fig. 7**

## INTERNATIONAL SEARCH REPORT

Internat. Application No.

PCT/EP 95/01163

A. CLASSIFICATION OF SUBJECT MATTER  
 IPC 6 B05B5/025 A61M15/00 A61M11/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X A	WO,A,92 15339 (PELTIER) 17 September 1992 see abstract; figures 2-5 see page 4, line 19 - line 25 ---	1-5,9-12 6-8
X	EP,A,0 523 962 (UNILEVER) 20 January 1993 see the whole document ---	1-5,9-11
X	US,A,4 749 125 (ESCALLON ET AL.) 7 June 1988 see abstract see column 8, line 11 - line 15; figure 11 ---	1-3,6,7
X	US,A,5 267 555 (PAJALICH) 7 December 1993 see abstract; figure 1 ---	1,8
X	EP,A,0 523 964 (UNILEVER) 20 January 1993 see page 6, line 28 - line 30; figure 2 ---	1-4,11
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

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International Application No

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,93 06937 (ICI) 15 April 1993 see abstract; figures 1,6 -----	1-3



# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 95/01163

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